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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,510	NANDABALAN ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020125*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibits A-C*.

DETAILED ACTION

Claims 1-21 are pending and examined on merits.

Information Disclosure Statement

The two information disclosure statements (initial IDS and supplemental IDS) were filed on 01/25/2002. A signed Form-1449 is attached with this Office action. The supplemental IDS says that copies and form 1449 are enclosed but the Office is unable to find either the copies or the form accompanying the supplemental IDS. The supplemental information disclosure statement filed on 1/25/2002 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered. The supplemental information statement filed 1/25/2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. If the copies and list are same for both two information disclosure statements (initial IDS and supplemental IDS), then applicant is kindly requested to state that in the next response because the two information disclosure statements with only one 1449 without explaining how they are related, is confusing.

Specification

The disclosure is objected to because of the following informalities: The specification at page 65 says that the instant applicant did not discover "MDM2" or SEQ ID NO:4. The sequence is from GenBank Accession No. M92424 and said GenBank Accession No. is the result of work by Oliner et al, published in 1992. Search of instant SEQ ID NO:4 in SwissProt protein database indeed indicates that Oliner et al deposited a 491 amino acid protein sequence. However, the instant SEQ ID NO:4 is missing Gly at #57 of MDM2 (see attached Exhibit A). Applicant is required to correct SEQ ID NO:4 in the drawing, sequence listing, CRF, etc. Appropriate correction is required.

For the purpose of this Office action, the Office will assume that instant SEQ ID NO:4 has Gly#57. However, this treatment does not relieve applicant the burden of responding to this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This written description rejection is made because claims 1-21 as currently construed appear to claim products with unknown structure(s); the instant specification does not teach how they look like. Claims 1-16, and 21 are interpreted as drawn to a purified complex of **two genuses** of polypeptides, and claims 17 and 18 are drawn to a chimeric polypeptide linking two genuses of polypeptides, wherein the first genus is drawn to polypeptides comprising an MDM2 binding domain of an MDMIP polypeptide, and the second genus is drawn to polypeptides comprising an MDMIP binding domain of an MDM2 polypeptide.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; and Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

First, a review of the language of the claims in respect to "MDMIP" indicates that the claims 1-21 could be interpreted as drawn to a genus i.e., any "MDMIP" protein that contains structurally unspecified MDM2 binding domain of MDMIP, for example, "comprising...an MDM2 binding domain of an MDMIP", "a polypeptide comprising the

amino acid sequence of an MDMIP polypeptide", "a human MDMIP polypeptide", or any "MDMIP" protein that **minimally contains SEQ ID NO:2** within it including any full length protein encoded from a full-open reading frame, which contains SEQ ID NO:2, any fusion constructs or the full-length isoform protein(s). The specification at pages 65-67 discloses SEQ ID NO:2, a deduced amino acids sequence from a novel cDNA (instant SEQ ID NO:1) isolated from a human fetal brain cDNA library using an N-terminal fragment (amino acid #1 to 216) of a human MDM2 as the bait in a yeast two hybrid screening system. Wong et al., (1997, Analytical Biochemistry, vol. 252, pages 33-39) teach that the yeast two-hybrid system is based on the ability of a pair of hybrid proteins, one containing a DNA binding domain and the other a transcription activation domain, to interact and activate transcription of reporter genes. The system is used to identify proteins that interact with a specific target or bait protein. The specification also discloses that instant SEQ ID NO:1 is 88 % identical to EST N28611. However, the identities were found only between nucleotides 87 and 317 of the isolated cDNA and nucleotides 83 and 372 of the isolated EST sequence, the isolated cDNA could not be extended in either direction. In summary, the isolated cDNA sequence is an EST sequence, and in turn, the disclosed SEQ ID NO:2 is a deduced amino acid sequence from an EST sequence. SEQ ID NO:2 is not a protein from a full-length ORF, but a fragment encoded by a EST. The instantly claimed invention is analogous to the hypothetical invention in Example 7 of in terms of written description analysis for the genus of polypeptide **comprising** "an MDM2 binding domain of an MDMIP

polypeptide". The analogous analysis to genus comprising SEQ ID NO:2 can be found at page 30-32 of PTO Written Description Guidelines (see attached Exhibit B).

The present claims 1-21 encompass the full-length proteins ("MDMIP") including differently spliced isoforms from a full length gene, which minimally contains SEQ ID NO:2. The specification discloses a single species i.e. a protein molecule consisting of SEQ ID NO:2 that is within the broadly drawn scope of the claimed genus. There is substantial variability among the species of proteins encompassed within the scope of the claims because SEQ ID NO:2 is only a fragment of any full-length protein species. They are structurally unrelated. A description of a genus of protein may be achieved by means of a recitation of a representative number of proteins, defined by amino acids sequences, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Since SEQ ID NO:2 is a deduced fragment from a single ESTs, the breath of the claims as reading on the full-length protein and isoforms of said protein, and a MDMIP polypeptide from pig and dog...etc. (see at page 27, 3rd paragraph of the specification) yet to be discovered, it is concluded that the written description requirement is not satisfied for the first genus i.e., MDMIP.

Second, a review of the language of the claims in respect to "MDM2" indicates that the claims 1-21 are drawn to a genus i.e., any "MDM2" protein that contains structurally unspecified MDMIP binding domain of MDM2. The specification at page 24 contemplates "MDMIP binding domain of MDM2" to be greater than any "5 amino acids"

of the art-known 491 amino acids MDM2 protein. The specification fails to teach which 5 amino acids of the art-known MDM2 protein is "MDMIP binding domain of MDM2" .

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the two claimed genuses.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the two encompassed genuses of proteins, given that the specification has only described SEQ ID NO: 2 and 4. Therefore, protein complex or chimeric protein **consisting** SEQ ID NO:2 and 4, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is interpreted as drawn to a purified complex MDMIP binding domain of MDM2 and MDM2 binding domain of MDMIP, and a chimeric polypeptide linking two polypeptides (i.e. MDM2 and MDMIP). This rejection has several aspects.

The disclosed use of the instantly claimed invention at page 6, for example, appears to be to detect MDM2 in a biological sample. The specification at pages 65-67 discloses SEQ ID NO:2, a deduced amino acids sequence from a novel cDNA (instant SEQ ID NO:1) isolated from a human fetal brain cDNA library using an N-terminal fragment (amino acid #1 to 216) of a human MDM2 as the bait in a yeast two hybrid screening system. However, the specification does not teach whether instant SEQ ID NO:2 is present in vivo, let alone forms a complex with MDM2 in vivo. Wang et al., (cited above) teach that a positive result of a protein-protein interaction in the two-hybrid screen does not necessarily mean the proteins interact in vivo. The interaction has to be verified to eliminate clones that are not biologically relevant (see page 33 left column, 3rd paragraph, and abstract). Wang et al., teach that two clones (out of 9 two-

hybrid positive clones) do not interact in vivo assay (see Table 1, and page 38). Nordgard et al also (2001, Biochimie, vol. 83, pages 969-71) also teach a false positive interaction in yeast two hybrid screening. Thus, based on interaction of SEQ ID NO:2 and SEQ ID NO:4 in yeast two hybrid screening, one of skill in the art would question whether SEQ ID NO:2 is a true in vivo binding partner of SEQ ID NO:4 or not. This part of rejection could be overcome by (1) presenting in vivo data demonstrating SEQ ID NO:2 is expressed in vivo, and (2) presenting in vivo data that SEQ ID NO:4 interacts in vivo with SEQ ID NO:2.

Second, the specification teaches use of the newly discovered protein i.e. MDMIP as binding partner of MDM2, but does not discloses any other uses of the said newly discovered protein. The specification at page 24, 2nd paragraph says that MDM2-bidnign domain is meant to include a full-length MDMIP polypeptide, and a 5 amino acids MDMIP binding polypeptide. However, the specification does not teach how to make the full-length protein or 5 amino acids MDMIP binding polypeptide. The specification at page 24, 5th paragraph also says that "MDMIP-binding domain" of MDM2 is at least 6 amino acids of an MDM2 polypeptide. However, the specification does not teach how to make 6 amino acids of an MDM2 polypeptide that forms complex with MDMIP comprising SEQ ID NO:2. The specification does not teach which 5 amino acids of MDMIP protein are involved in complex with MDM2, or which 6 amino acids of MDM2 are involved in complex formation with an MDMIP protein. One cannot extrapolate the teaching of the specification to the claims because MDM2 and MDMIP are proteins. It is well known in the art that even slight modifications in a peptide or

protein structure and can have significant and unpredictable effects on biological activity. Bowie et al., (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al., further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid (including conservative substitutions) in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or even with conservative glutamic acid sharply reduced the biological activity of the mitogen. These

references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. The specification does not teach the specific structures responsible for binding of MDM2 to MDMIP (or vice versa), nor provide guidance as to what changes in the structure can be made complex formation activity of the two proteins. The specification does not teach which 5-10 % of amino acids from SEQ ID NO:2 could be changed in order to maintain the complex formation activity. The specification at the paragraph bridging page 24 and 25 says that procedures for identifying regions within SEQ ID NO:4 that is able to bind specifically to an MDMIP polypeptide could by identified. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

The specification provides insufficient guidance, and provides no working examples of in vivo complex formation which would provide guidance to one skilled in the art to use the claimed invention without undue experimentation, and no evidence has been provided which would allow one of skill in the art to predict the whether MDM2 could be detected by using the newly discovered MDNIP protein with a reasonable expectation of success. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 21 recites "a pharmaceutical". Inherent in pharmaceutical is in vivo use.

The specification at page 47, 1st paragraph speculates that the therapeutic of the present invention may be useful in treatment of cancers. Only disclosure in the instant specification is that a new cDNA is isolated from two yeast hybrid screening using the N-terminal fragment of a human MDM2 protein. Based on this disclosure, one of skill would have question the efficacy of the claimed pharmaceutical for treating cancer because cancer treatment is not a trivial matter i.e. an unpredictable art.

One cannot extrapolate the teaching of the specification to the claim because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Max, J., (Science. 2004 Jan 2;303: 23-5) teaches the current state of cancer treatment targeting MDM2 protein. Max teaches that MDM2 is a natural inhibitor of a tumor suppressor p53 protein (see 2nd paragraph at page 23) and researchers are trying to develop anti-cancer agents that prevent MDM2 binding to p53. This indicates presence of more MDM2 in vivo is bad. Thus, one in the art would question the efficacy of pharmaceutical comprising complex of MDM2 and MDMIP.

Instead of treating cancer, the claimed composition would make cancer grow better by titrating out the tumor suppressor p53 protein. Considering the known unpredictability of the cancer treatment art, in the absence of experimental evidence, and limited guidance in the specification, one of skill in the art would have difficult accepting the assertion that claimed pharmaceutical composition would be used as pharmaceutical for cancer treatment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 11-19, and 21 rejected under 35 U.S.C. 102(b) as being anticipated by any one of US Pat. 5,411,860 (May 2, 1995) as (evidenced by Promega Notes Magazine Number 57, 1996, p.27), Brown et al (1993, Molecular and Cellular Biology, vol. 13, pages 6849-6857), or Kussie et al (1996, Science, vol. 274, pages 948-952).

This art rejection is made because claims 1-7, 11-19, and 21 as currently construed read on a purified complex that had been known to public before the effective filing date of the instant application. The specification at page 2, lines 21-24 broadly defines "MDMIP" is a protein "based on its ability to bind to the MDM2 polypeptide." The specification at page 22, lines 21-23 appears to define "MDMIP" to be any protein or peptide that binds to MDM2 and SEQ ID NO:2 is one example of MDMIP. Based on these broad definitions of "MDMIP", claims 1-7, 11-19, and 21 are interpreted as drawn

to a purified complex comprising an interacting domain of MDM2 and MDM2 interacting domain of MDMIP, wherein an interacting domain of MDM2 is SEQ IS NO:4 in claims 11, and 12, and wherein claim 13 specifies that MDM2 is labeled and claim 14 specifies that MDMIP is labeled. Claims 17-19 are broadly drawn to unspecified six or more amino acids of MDM2 linked to unspecified six or more amino acids of MDMIP, thus claims 17-19 read on any polypeptide longer than a 12-mer polypeptide because the claims 17-19 do not even say the claimed sequences comes from 6 or more consecutive polypeptide sequence of MDM2.

Brown et al., teach a purified complex of MDM2 and p53 (MDMIP), with a label at p53 and MDM2 at page 6850-1 under "Materials and Methods" and also at Fig. 5-10. See. Fig. 11 for MDM2 sequence. The wild type MDM2 appears to comprise instant SEQ ID NO:4. See the attached sequence alignment (Exhibit A). Also note that instant SEQ ID NO:4 has missing Gly residue from the known wild-type sequence. See the objection of the specification above for further detail. Thus, instant claims 1-7, 11-16, 21 read on the labeled purified MDM2-p53 protein complex, for example, shown at Fig. 5 of Brown et al., and instant claims 17-19 read on any one of the various proteins disclosed because of the broad claim construction without specific amino acid structure. As for claim 21, the preamble "pharmaceutical" is not given a patentable weight for art rejection.

US Pat. 5,411,860 also teaches a purified complex of MDM2 and p53 (MDMIP), with a label at p53 and MDM2 at columns 7-9, and Fig. 2. The '860 patent under Example 2 says that the proteins were synthesized in T7 polymerase and translated in a

rabbit reticulocyte (Promega) and then purified with various antibodies; the proteins i.e. hMDM2 and p53 are labeled with S^{35}. See the attached Promega Notes Magazine Number 57, 1996, p.27 for protein labeling with the isotope. Note also the sequence alignment (Exhibit C). Instant claims 17-19 read on any one of the various proteins disclosed because of the broad claim construction without specific amino acid structure. As for claim 21, the preamble "pharmaceutical" is not given a patentable weight for art rejection.

Kussie et al., also teach a purified complex of MDM2 and p53 (MDMIP) at Fig. 2 for example. See the sequence alignment (Exhibit A) showing that instant SEQ ID NO:4 with the missing Gly #52 is the wild-type MDM2. Thus, instant claims 1-7, 11-16, and 21 read on the complex shown at Fig. 2 A, for example, and claim 17-19 read on the wild type MDM2 used for the crystallization. The specification does not define "labeled". So the Office refers to Merriam-Webster Online dictionary downloaded on 5/2/04 for "labeled", which is defined as "to affix a label" to "distinguish". Therefore the heavy atom derivative of the MDM2 and p53 for crystal structure determination appears to meet the limitation of "labeled" according to the dictionary definition.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne C Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642